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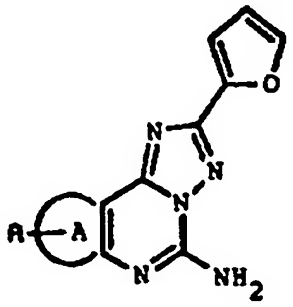
(54) Title: 1,2,4-TRIAZOLO[1,5-c]PYRIMIDINE HETEROCYCLIC ANALOGUES HAVING ANTAGONISTIC ACTIVITY ON ADENOSINE A_2 RECEPTOR

(57) Abstract

The compounds of formula (I) wherein R and A have the meanings given in the specification, are endowed with selective A_2 adenosine receptor antagonistic activity.



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1,2,4-TRIAZOLO[1,5-c]PYRIMIDINE HETEROCYCLIC ANALOGUES HAVING ANTAGONISTIC ACTIVITY ON ADENOSINE A_2 RECEPTOR

The present invention relates to compounds having antagonistic activity on adenosine A_2 receptor.

Adenosine is known to modulate a number of physiological functions. At the cardiovascular system level, adenosine is a strong vasodilator and a cardiac depressor. On central nervous system, adenosine induces sedative, anxiolytic and antiepileptic effects. On the respiratory system, adenosine induces bronchoconstriction. At the kidney level, it exerts a diphasic action, inducing vasoconstriction at low concentrations and vasodilatation at high doses. Adenosine acts as a lipolysis inhibitor on fat cells and as an antiaggregant on platelets (Stone T.W., Purine receptors and their pharmacological roles. In: Advances in drug research. Academic Press Limited, 1989, 18, 291-429; Progress Cardiovasc. Dis. 1989, 32, 73-97).

A number of studies showed adenosine actions are mediated by two subtypes of receptors which are located on the cell membrane: an high-affinity one, inhibiting the activity of the enzyme adenylate cyclase (A_1 receptor), and a low-affinity one, stimulating the activity of the same enzyme (A_2 receptor) (J. Med. Chem. 1982, 25, 197-207. Physiol. Rev. 1990, 70(3), 761-845. J. Med. Chem. 1992, 35, 407-422).

Intense research efforts have made it possible to identify and develop analogs to adenosine able to interact as agonists with the A_1 and A_2 receptor. As far as the antagonists are concerned, it is known that some

compounds with a xanthine structure are selective antagonists for the A_1 receptor.

(J. Med. Chem., 1992, 25, 407-422). New compounds of pharmacological interest which possess an high antagonistic action for the A_2 receptor have not yet been found.

The knowledge available on the physiological role of adenosine and its involvement in some pathological processes suggests that selective antagonists for the A_2 receptor can be of pharmacological interest. At the level of the central nervous system, antagonistic A_2 compounds should stimulate various cerebral functions and so possess antidepressive and stimulating properties for the cognitive functions. Moreover, numerous data show that the A_2 receptors are present in high density in the basal ganglia of which the importance in the control of movement is known. Hence the hypothesis that A_2 antagonists can improve motor-deficiency due to neurodegenerative processes at the level of important cerebral nuclei. It follows that A_2 receptor antagonists could be useful in the treatment of neurodegenerative pathologies. Amongst these are included Parkinson's disease, senile dementia as in Alzheimer's disease and psychosis of an organic origin (Drug Dev. Res., 1993, 28, 381-385).

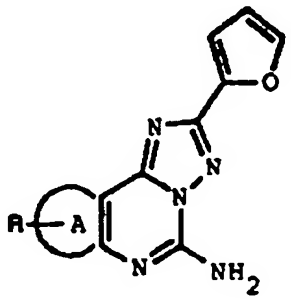
At a peripheric level, A_2 receptor antagonists could stimulate the respiratory functions and therefore have a therapeutic effect in the treatment of bronchospasm and more generally asthma. Moreover, with regard to the effects at a cardiovascular or renal level, an advantageous activity on renal flow can be envisaged

and therefore the possibility of the treatment of renal insufficiency and of various cardiovascular disturbances.

Some reference compounds interacting with A_2 receptor, even though in a not selective way, are known.

5-Amino-9-chloro-2(2-furyl)1,2,4-triazolo[1,5-c]quinazoline, named CGS 15943 (J. Med. Chem., 1988, 31, 1014-1020) and 4-amino-8-chloro-1-phenyl(1,2,4)-triazolo(4,3-a)quinoxaline, named CP 66,713 (J. Med. Chem., 1990, 33, 2240-2254) are compounds having a good affinity for A_2 receptor, but also active on A_1 receptor. Only recently, xanthine derivatives have been found, e.g. (E)-1,3-dialkyl-7-methyl-8-(3,4,5-trimethoxystyryl)xanthines (J. Med. Chem., 1992, 35, 2342-2345), which seem to have a selective antagonistic activity on A_2 receptors. However, the pharmacological profile thereof is unknown.

The compounds of the invention have the following general formula I:



I

in which:

A is a pyrazole, imidazole or triazole ring;

R is hydrogen; C_1-C_8 alkyl; C_3-C_7 alkenyl, C_3-C_7 alkynyl; C_3-C_7 cycloalkyl; C_1-C_5 alkyl substituted with

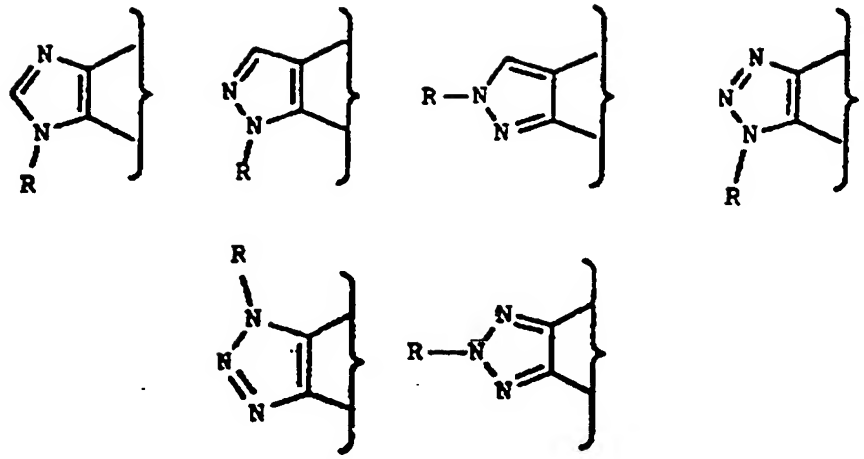
one or more halogen atoms, hydroxy groups, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl, groups of formula $-NR_1R_2$, $-CONR_1R_2$; aryl optionally substituted with halogen atoms, C_1-C_4 alkoxy groups, C_1-C_4 alkyl, nitro, amino, cyano, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, carboxy, carboxyamido; C_7-C_{10} aralkyl in which the aryl moiety can be substituted with one or more of the substituents indicated above for the aryl group; a group of formula $-(CH_2)_m$-Het, wherein Het is a 5-6 membered aromatic or non aromatic heterocyclic ring containing one or more heteroatoms selected from N, O, S and m is an integer from 1 to 5;

R_1, R_2 which are the same or different, are hydrogen, C_1-C_5 alkyl, C_7-C_{10} aralkyl, phenyl, or taken together with the nitrogen atom they are linked to, they form an azetidine ring or a 5-6 membered heterocyclic ring containing one or more heteroatoms such as N, O, S and n is an integer from 2 to 5, with the proviso that, when A is a pyrazole or imidazole, R is different from fluorobenzyl.

The disclaimed compounds are disclosed in Eur. J. Med. Chem., 1993, 28, 569-576,

The invention also comprises the pharmaceutically acceptable salts of the compounds of general formula I.

The possible meanings of A can be represented by the following structural formulae:



In compounds of formula I, examples of C_1-C_8 alkyl groups comprise preferably methyl, butyl and isopentyl.

Examples of C_3-C_7 cycloalkyl groups are cyclopropyl, cyclopentyl, cyclohexyl.

Examples of C_1-C_5 alkyl groups substituted with C_3-C_7 cycloalkyl groups are cyclohexylmethyl, cyclopentylmethyl, 2-cyclopentylethyl.

Examples of substituted C_1-C_5 alkyl groups comprise 2-hydroxyethyl, 2-methoxyethyl, trifluoromethyl, 2-fluoroethyl, 2-chloroethyl, 3-aminopropyl, 2-(4-methyl-1-piperazine)ethyl, 2-(4-morpholinyl)ethyl, 2-aminocarbonylethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl. Aryl is preferably phenyl, optionally substituted with chlorine, fluorine atoms, methoxy, nitro, cyano, methyl, trifluoromethyl, difluoromethoxy groups. Examples of 5-6 membered heterocyclic groups containing N, O, S comprise piperazinyl, morpholinyl, thiazolyl, pyrazolyl, pyridyl, furyl, thienyl, pirrolyl, triazolyl, tetrazolyl. Examples of C_7-C_{10} aralkyl groups comprise benzyl or phenetyl optionally substituted by one or more substituents selected from chlorine, fluorine atoms, methoxy, nitro, cyano, methyl, trifluoromethyl, difluoromethoxy groups.

Preferably, R is hydrogen, C_1-C_8 alkyl, aryl or C_7-C_{10} aralkyl optionally substituted, preferably with halogen atoms.

Particularly preferred compounds I are those in which R is a phenetyl group in which the phenyl ring may optionally be substituted by one or more substituents selected from chlorine, fluorine atoms, methoxy, nitro, cyano, methyl, trifluoromethyl, difluoromethoxy groups.

The compounds of general formula I have advantageous biochemical and functional properties related to their antagonistic action on the A_2 adenosine receptor, compared with the reference compounds CGS 15943 and (5-amino-8-(4-fluorobenzyl)-2-(2-furyl)-pyrazolo [4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine), disclosed in Eur. J. Med. Chem., 1993, 28, 569-576 and hereinafter referred to as 8FB-PTP. The effects of the disclosed A_2 receptor antagonists may be demonstrated in one or more of the following standard in vitro and/or in vivo tests.

IN VITRO TESTS

Receptor binding

This test involves the ability of adenosine antagonists to displace radiolabeled agonists from A_1 and A_2 adenosine binding sites in membrane preparations from rat brain.

The rat cerebral tissue (whole brain and striatum) was from male Sprague-Dawley rats weighing 150-200 g. A_1 and A_2 receptor binding assays were performed according to Bruns et al. (Proc. Natl. Acad Sci. U.S.A., 1980, 77, 5547-5551) and Jarvis et al. (J.

Pharmacol. Exp. Ther., 1989, 251, 888-893), using [3H]N6-cyclohexyladenosine ([3H]CHA) and [3H]2-[p-(2-carboxy ethyl)-phenetylamino]-5'-N-ethylcarboxamido-adenosine ([3H]CGS 21680) as radioligands, respectively.

The test compounds were dissolved in dimethylsulphoxide (DMSO) and then diluted with assay buffer to give the test solutions. The final concentration of DMSO did not exceed 1% by volume, at which level it did not affect radio ligand binding to the membrane receptor.

The selectivity for A_2 receptors was evaluated by comparing the affinities of each compound for A_1 and A_2 receptors. A marked relationship between binding affinities and physiological effects modulated by adenosine receptors has been demonstrated elsewhere (Conti et al., Naunyn-Schmied. Arch. Pharmacol., 1993, 348,108-112).

The disclosed compounds, described in formula I, have marked A_2 receptor affinity with Ki values ranging from 1 nM to 100 nM (Table). Moreover, some compounds show A_2 versus A_1 selectivity higher than that of the reference compounds CGS 15943 and 8FB-PTP. In particular, compound 341 has a selectivity for A_2 versus A_1 receptors of about 50-fold.

Rat aorta and bovine coronary artery

The A_2 adenosine antagonistic activity of these compounds was investigated by evaluating their ability to counteract vasodilation induced by adenosine agonists in vascular tissues, such as rat aorta and bovine coronary arteries, after precontraction with 3μM

of prostaglandin F2α. The method used to test adenosine agonists is described elsewhere (Conti et al.,Naunyn-Schmied. Arch. Pharmacol., 1993, 348, 108-112). Cumulative dose-response curves were constructed, using increasing concentration of NECA (1 nM-10 uM), in the absence or presence of the antagonist.

Many of the test compounds, at concentrations ranging from 0.03 to 1μM, were able to shift to the right the dose-response curves of the agonist in a concentration-dependent manner.

Rat atria

The ability of the disclosed compounds to antagonize the negative chronotropic effect induced by A_1 receptor agonists was tested on isolated rat atria, whose beating rate is known to be modulated by A_1 adenosine receptors. The method used to test adenosine agonists is described elsewhere (Conti et al., Naunyn-Schmied. Arch. Pharmacol., 1993, 348, 108-112). The decrease in atrial rate evoked by cumulative addition of the A_1 selective agonist, 2-chloro-N^6-cyclopentyladenosine (CCPA) was measured. The dose-response curves of the agonist was then repeated in the presence of the antagonist. The receptor selectivity of test compounds can be evaluated by comparing the activities of each compound in antagonizing either A_2 (vasodilation)- or A_1 (heart rate)-mediated responses.

Some of the disclosed compounds were found to have little or no effects on the A_1-mediated response in isolated rat atria. Inparticular, compound 341 is ineffective in this functional model, thus confirming

its A_2 versus A_1 selectivity observed from binding studies.

IN VIVO TESTS

Behavioral effects

The behavioral response to treatment with different doses (ranging from 1 to 100 mg/Kg) of the test compounds administered parenterally were evaluated in Swiss mice using the classic "Irwin test" (Irwin, Psychopharmacologia, 1968 13, 222-257). Behavior, autonomic and neurological functions of the animals were assessed through 36 different parameters evaluated during observation sessions at 1, 2, 4 and 6 h after drug administration. The animals were observed until 24 h after administration for checking mortality.

The test compounds produced no mortality and only tended to stimulate central nervous system activity.

Hemodynamic tests

In adult male spontaneously hypertensive rats, some of the disclosed compounds were administered parenterally at increasing doses (1-30 mg/Kg) and their ability in antagonizing the bradycardic and hypotensive effects induced by A_1 and A_2 adenosine receptor agonists, respectively, was measured. Systolic blood pressure and heart rate were measured in conscious animals by the tail-cuff method as described elsewhere (Monopoli et al., Arch. Int. Pharmacodyn. Ther., 1987, 286, 246-254).

The test compounds antagonize hypotension induced by A_2 agonists with a potency similar or higher than that of the reference compounds CGS 15943 and 8FB-PTP, whereas some of them antagonize the

A_1-mediated responses slightly and only at higher doses.

TABLE - BIOLOGICAL ACTIVITY OF A SERIES OF NEW A2 ADENOSINE RECEPTOR ANTAGONISTS

Compound N°	Binding[a] A_1 Ki (nM)	Binding[a] A_2 Ki (nM)	Selectivity A_1/A_2
DCPCX	1.5	727	0.002
CGS 15943	6.4	1.2	5.3
8FB-PTP	3.3	1.2	2.8
N° 292	237	9.0	26.3
N° 294	31.2	2.4	13.0
N° SP 319	120	12.6	9.5
N° SP 320	5.8	1.9	3.1
N° SP 340	61.5	13.8	4.4
N° SP 341	123	2.4	51.3
N° SP 363	18.6	2.6	7.2
N° SP 375	4.7	1.5	3.2
N° SP 376	42.6	7.1	6.0

[a]Inhibition of [^{3}H]CHA binding (A_1) in rat whole brain homogenates or [^{3}H]CGS 21680 binding (A_2) in rat striatal homogenates.

- DPCPX (8-cyclopentyl-1,3-dipropylxanthine) is a standard A_1 selective antagonist (Bruns et al., Naunyn-Schmied. Arch. Pharmacol., 1987, 335, 59-63).
- CGS 15943 (5-amino-9-chloro-2-(2-furyl)1,2,4-triazolo[1,5-c]quinazoline is a reference slightly selective A2 antagonist (Francis et al., 1988, J.

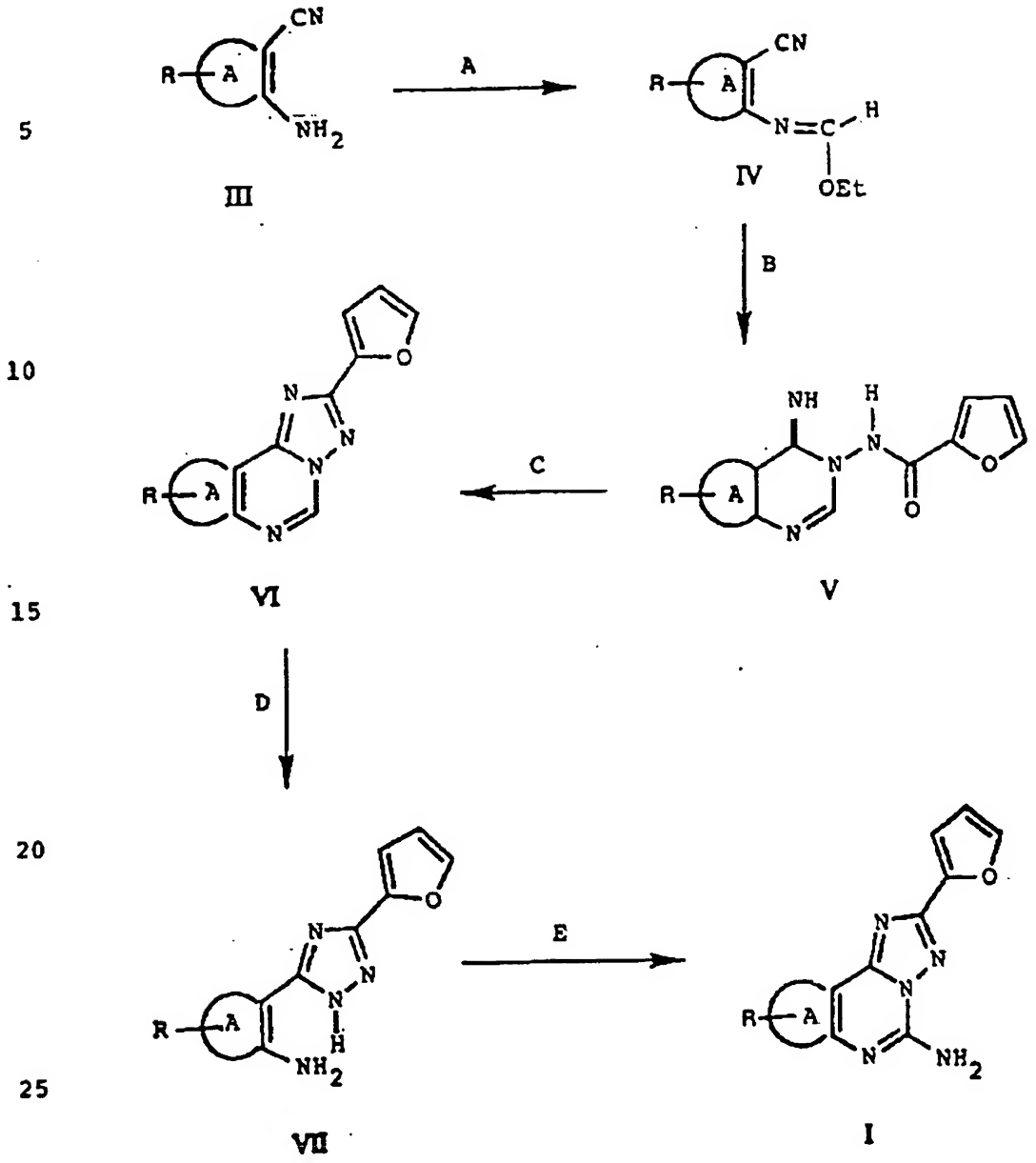
Med. Chem., 31, 1014-1020).

- 8FB-PTP (5-amino-8-(4-fluorobenzyl)-2-(2-furyl)-pyrazolo[4,3-4e]-1,2,4-triazolo[1,5-c]pyrimidine) is a reference slightly selective A2 antagonist (Gatta et al., Eur. J. Med. Chem., 1993, 28, 569-576).

For the envisaged therapeutical uses, compounds I will be formulated as suitable pharmaceutical compositions, which can be administered, for example, by the oral, parenteral or transdermal routes, using known techniques and excipients, as described for example in Remington's Pharmaceutical Sciences Handbook, Mack Pub. Co., NY, USA, XVII ed. The daily dosage will depend, of course, on many factors (severity of the pathology to treat, patient conditions, toxicology and pharmacokinetic of the selected compound) but generally it will range from 0,01 to 10 mg/kg body weight, preferably from 0,1 to 1 mg/kg, optionally subdivided in more administrations. Examples of pharmaceutical compositions comprise capsules, tablets, solutions, syrups, vials, controlled-release forms, transdermal forms (cerotti) and the like.

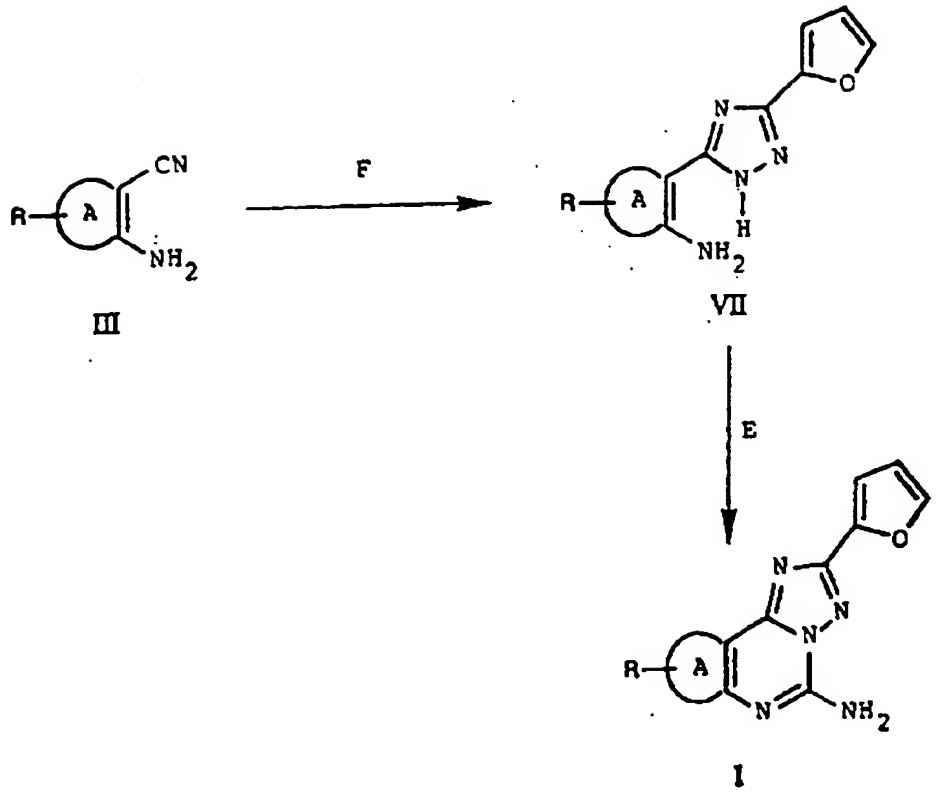
The compounds of the invention were prepared according to the synthetic schemes reported below.

Scheme I



Reagents: A) triethyl orthoformate; B) 2-furoic acid hydrazide, 2-methoxyethanol; C) PhOPh, 260°C; D) 10% HCl, under reflux; E) cyanamide, pTsOH, N-methylpyrrolidone

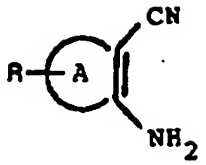
Scheme II



Reagents: F) furoic acid hydrazide, diphenylether; E) cyanamide, pTsOH, N-methylpyrrolidone.

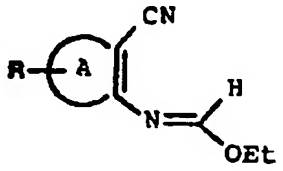
The compounds of formula I of the invention can be prepared through either an indirect route described in Scheme I or a direct route described in Scheme II.

Suitable starting materials for both schemes are the heterocyclic ortho-amino nitriles of formula III, generally prepared according to synthetic procedures known in literature and reported in the book by E.C.Taylor and A.McKillop (vol. 7 of the series Advances in Organic Chemistry, Ed. Interscience, 1970).



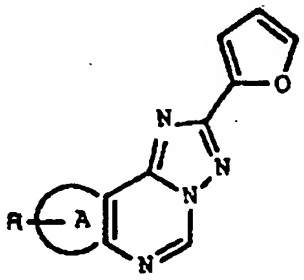
III

Ortho-amino nitriles III are transformed into the corresponding imidates of formula IV by reaction with an ethyl orthoformate excess at the reflux temperature for 8-10h. The reaction, after evaporation of the ethyl orthoformate, leads to the substantially pure corresponding imidates IV in a high yield as evidenced by the IR and ^1H NMR analysis on the crude reaction products.



IV

The imidates of formula IV are then subjected to a sequence of two reactions allowing to obtain the tricyclic structures of formula VI in a high yield.

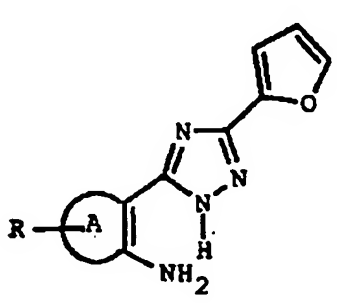


VI

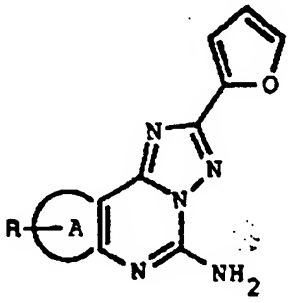
The reaction sequence comprises: a) reaction with 2-furoic acid hydrazide in a 2-methoxyethanol solution at the reflux temperature for 8-10h, to obtain the intermediates compounds of formula V; b) thermal cyclization of the latter to corresponding compounds of for-

mula VI, by heating in diphenyl ether at the temperature of 260°C for 0.5-1h.

The tricyclic compounds VI are then hydrolyzed with 10% HCl at the reflux temperature for 1-3h to give triazoles VII, which are finally cyclized to desired compounds I with cyanamide in N-methyl pyrrolidone at the reflux temperature and in the presence of para-toluenesulfonic acid (Scheme I).



VII

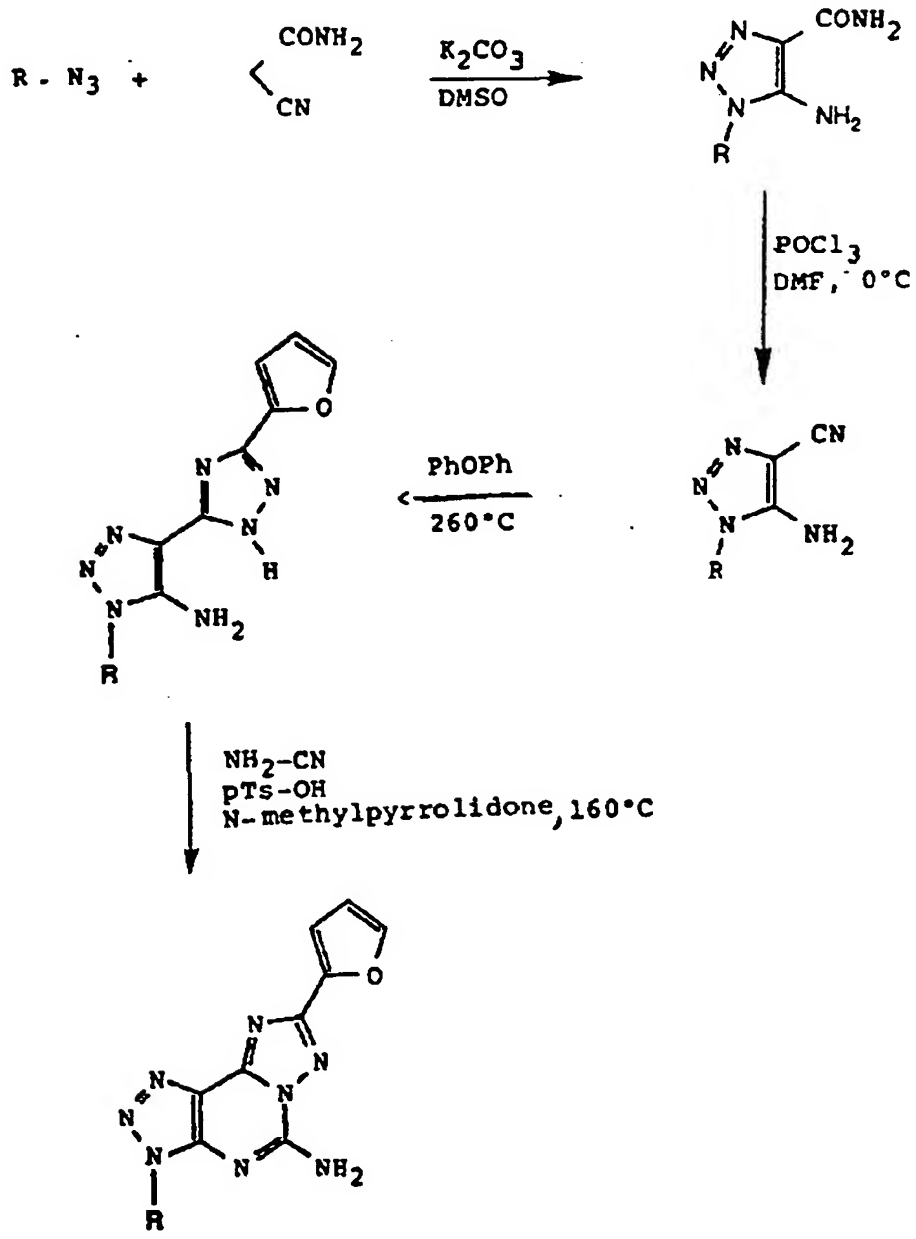


I

In some cases, triazoles VII can be obtained directly heating in diphenyl ether ortho-amino nitriles III with 2-furoic acid hydrazide. Triazoles VII are then cyclized as described above (Scheme II). In the following schemes III, IV and V, the synthesis of the compounds I in which A is a triazole ring is reported in more detail.

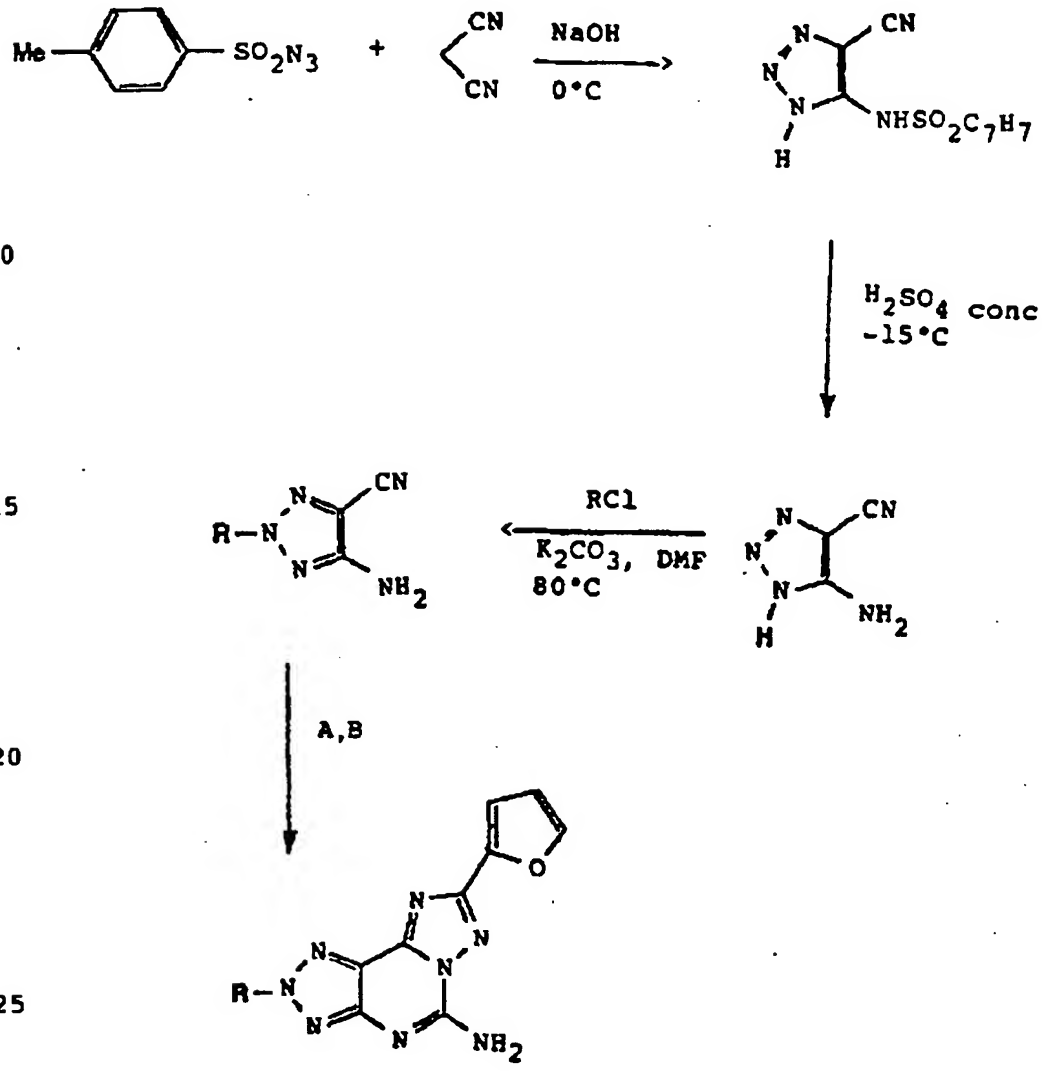
Scheme III

Synthesis of 5-amino-7-substituted-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine derivatives



Scheme IV

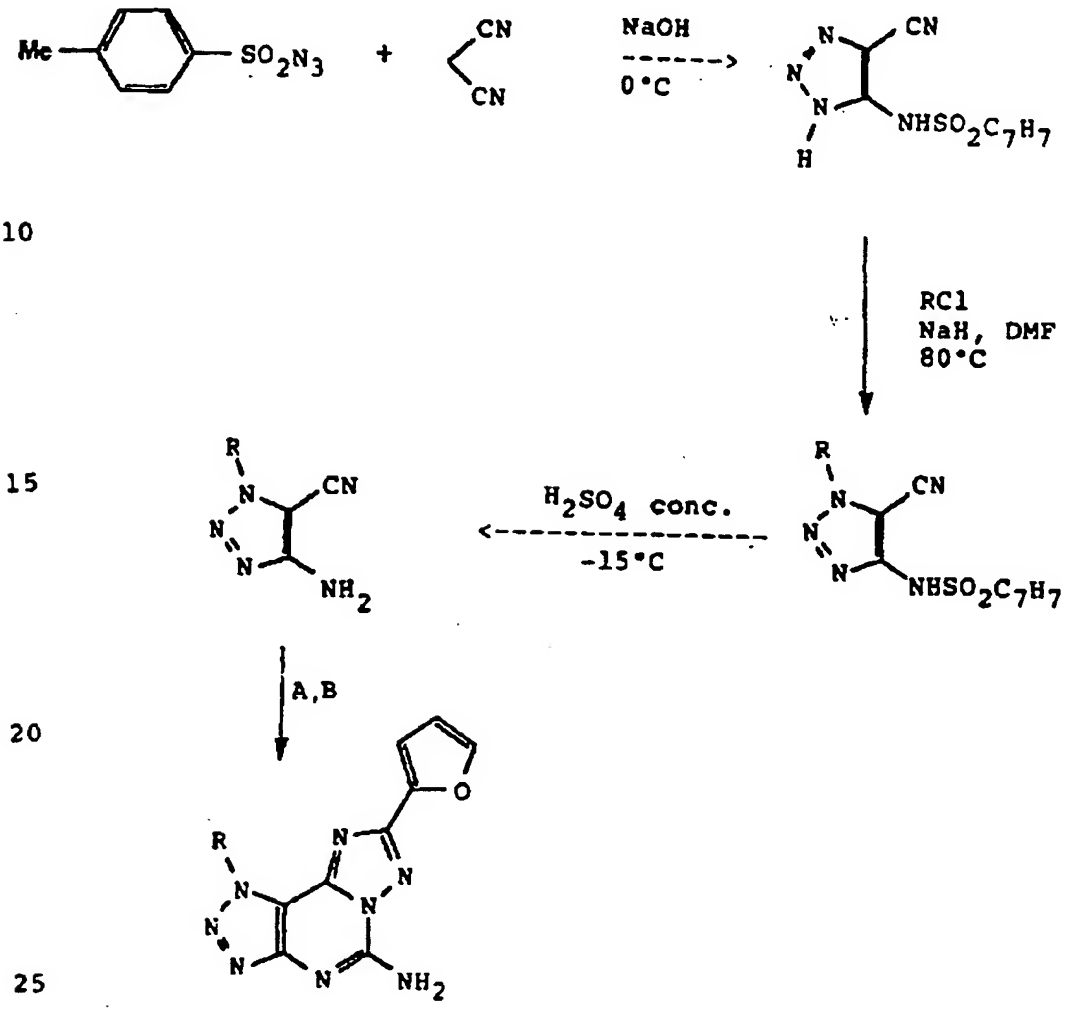
Synthesis of 5-amino-8-substituted-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine derivatives



Reagents: A) furoic acid hydrazide, PhOPh, 260°C, B) NH_2CN, pTsOH, N-methylpyrrolidone.

Scheme V

Synthesis of 5-amino-9-substituted-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine derivatives



Reagents: A) furoic acid hydrazide, PhOPh, 260°C, B) NH_2CN, pTsOH, N-methylpyrrolidone.

The following examples illustrate the invention in more detail.

Example 1

According to the procedures described in J. Org. Chem. 1956, 21, 1240; J. Am. Chem. Soc. 1956, 78, 784 and the references herein cited, the following compounds are prepared, starting from commercially available ethoxy-methylene malondinitrile and N1-substituted hydrazines, which also are mainly commercially available:

1-methyl-4-cyano-5-aminopyrazole
1-n-butyl-4-cyano-5-aminopyrazole
1-isopentyl-4-cyano-5-aminopyrazole
1-(2-cyclopentyl)ethyl-4-cyano-5-aminopyrazole
1-hydroxyethyl-4-cyano-5-aminopyrazole
1-phenyl-4-cyano-5-aminopyrazole
1-tert-butyl-4-cyano-5-aminopyrazole
1-phenylethyl-4-cyano-5-aminopyrazole
1-(2-chlorophenyl)-4-cyano-5-aminopyrazole.

Example 2

Starting from 4-cyano-5-aminopyrazole, prepared according the procedure reported in Chem. Pharm. Bull. 1970, 18, 2353 or in J. Heterocyclic Chem. 1979, 16, 1113, 1-substituted 4-cyano-3-aminopyrazoles can be prepared by direct alkylation with the corresponding alkyl halide in dimethylformamide at 80°C for 1-2h in the presence of anhydrous potassium carbonate. From the reaction mixture, containing the two N_1 and N_2 alkylated position isomers in an about 1:2 ratio, the N_2 isomer can be isolated by a single crystallization or column chromatography on silica gel eluting with

ethyl acetate and petroleum ether mixtures. Using said procedures, the following compounds were prepared:

1-methyl-4-cyano-3-aminopyrazole

1-butyl-4-cyano-3-aminopyrazole

1-benzyl-4-cyano-3-aminopyrazole

1-isopentyl-4-cyano-3-aminopyrazole

1-phenylethyl-4-cyano-3-aminopyrazole

Example 3

a) A suspension of anhydrous potassium carbonate (30 mmols) in DMF (50 ml) is added with 3-amino-4-cyano-pyrazole (20 mmols), heating to a temperature of 80°C for 30 minutes. The suspension is added with phenethyl bromide (25 mmols) and is heated to 80°C for 2h. After cooling to room temperature, the mixture is evaporated to dryness under vacuum and the resulting residue is taken up with distilled water (100 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts are dried over anhydrous sodium sulfate and evaporated to dryness under vacuum.

The resulting residue consists of a 1:3 mixture of 1-phenylethyl-4-cyano-5-aminopyrazole (20%) and of 1-phenylethyl-4-cyano-3-aminopyrazole (60%) which may be used as such in Example 4 or chromatographed on silica gel column eluting with an ethyl acetate/hexane mixture to give:

1-phenylethyl-4-cyano-5-aminopyrazole m.p. 172-173°C; (20%);

^{1}H-NMR (DMSO-d_6): 3.04 (t, 2H); 4.12 (t, 2H); 5.85 (sb, 2H); 7.21-7.30 (m, 5H); 7.41 (s, 1H); e 1-ß-phenylethyl-4-cyano-3-aminopyrazole m.p. 98-100°C (60%); ^{1}H-NMR ($CDCl_3$): 3.07 (t, 2H); 4.10 (t, 2H); 4.23

(sb, 2H); 7.17 (s, 1H); 7.00-7.28 (m, 5H).

b) A solution of 1-ß-phenylethyl-4-cyano-5-aminopyrazole (20 mmol)in triethylorthoformiate (40 ml) is refluxed under nitrogen for 8 h.

The excess orthoformiate is evaporated to dryness under vacuum and the residual yellow oil is dissolved in ethyl ether and percolated onto silica gel to give the corresponding iminoether (87% yield). The residue obtained after orthoformiate evaporation is practically pure and is directly used in the following step. A solution of the iminoether (20 mmol) and of 2-furoic acid hydrazide (2.5 g, 22 mmol) in 2-methoxyethanol (50 ml) is refluxed for 5-10 h. After cooling, the solution is evaporated to dryness to give an oily residue which is subjected to thermal cyclization in diphenylether (50 ml) using a Dean-Stark apparatus so as to azestropically remove water formed during the reaction. After 1.5 h, the reaction is checked in TLC (ethyl acetate:petroleum ether 2:1) and when the starting compound is completely absent, the mixture is cooled and added with hexane. The resulting precipitate is filtered and crystallized to give 7-(ß-phenylethyl)-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazole[1,5-c]pyrimidine m.p. 174-175°C (20%) 1H-NMR (DMSO-d_6):3.23 (t,2H); 4.74 (t, 2H); 6.75 (s, 1H); 7.14-7.17 (m, 5H); 7.28 (s, 1H); 7.98 (s, 1H); 8.53 (s, 1H); 9.56 (s, 1H).

In a similar way, starting from 1-ß-phenylethyl-4-cyano-3-aminopyrazole, 8-(ß-phenylethyl)-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazole[1,5-c]pyrimidine m.p. 268-270°C (60%) 1H-NMR (DMSO-d_6): 3.32 (t, 2H); 4.72 (t, 2H); 6.73 (s, 1H), 7.23 (m, 5H); 7.95 (s, 1H); 8.8

(s, 1H); 9.41 (s, 1H) is obtained.

c) A suspension of a compound VI of step b) (10 mmol) in 10% HCl (5.0 ml) is refluxed under stirring for 3 h. After cooling, the solution is alkalinized with concentrated ammonium hydroxide at 0°C and the resulting precipitate is filtered or extracted with ethyl acetate (3 x 100 ml), dried and evaporated to dryness under vacuum, to give the corresponding 1-(ß-phenylethyl)-4-[3(2-furyl)-1,2,4-triazol-5-yl]-5-amino-pyrazole m.p. 175-176°C; ^{1}H-NMR (DMSO-d_6):3.15 (t, 2H); 4.48 (t, 2H); 5.78 (s, 1H), 6.37 (s, 1H); 6.68 (s, 1H); 7.1 (s, 1H); 7.27-7.28 (m, 5H); 7.82 (s, 1H); 14.51 (sb, 2H): in a similar way 1-(ß-phenylethyl)-4-[3(2-furyl)-1,2,4-triazol-5-yl]-3-aminopyrazole (m.p. 205-206°C); 1H-NMR (DMSO-d_6): 3.12 (t, 2H); 4.46 (t, 2H); 5.75 (s, 1H); 14.41 (sb, 2H) is obtained.

d) Cyanamide (60 mmol) is added to a suspension of an amine of formula VII prepared in step c) (10 mmol) in N-methylpyrrolidone (40 ml) followed by p-toluensulfonic acid (15 mmol).

The mixture is heated to 160°C under stirring. After 4 h a second portion of cyanamide (60 mmol) is added and heating is continued overnight. The mixture is then treated with hot water (200 ml) and the precipitate is filtered, washed with water and crystallized from ethanol to give the corresponding 5-amino-7-(ß-phenylethyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazo-le[1,5-c]pyrimidine m.p. 225-226°C 1H-NMR (DMSO-d_6): 3.21 (t, 2H); 4.51 (t, 2H); 6.65 (s, 1H); 7.1-7.44 (m, 5H, arom and 1H); 7.78 (s, 1H); 7.89 (sb, 2H); 8.07 (s, 1H) (Compound 341): in a similar way 5-amino-8-(ß-

phenylethyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazole[1,5-c]pyrimidine m.p. 212-213°C 1H-NMR (DMSO-d_6): 3.21 (t, 2H); 4.53 (t, 2H); 6.7 (s, 1H); 7.1-7.4 (m, 5H, arom and 1H); 7.65 (sb, 2H); 7.93 (s, 1H); 8.45 (s, 1H) (Compound 375) is obtained.

Example 4

A suspension of potassium carbonate (0.23 mole) in DMSO (70 ml) is added subsequently with cyanoacetamide (70 mmols) and p-fluorobenzylazide (54.5 mmols). The resulting solution is stirred at room temperature for 1h and then poured into a large volume of water (1.5 l). The separated solid is filtered, washed with water and dried in oven at 70°C to give 1(p-fluorobenzyl)-4-carboxamido-5-amino-1,2,3-triazole (96% yield).
M.p.: 198-199°C; ^{1}H NMR (DMSO-d_6): 7.5-7.1 (m,6H); 6.4 (s,2H); 5.4 (s,2H).

An amide suspension (0.005 mole), stirred and cooled to 0°C, in DMF (5 ml) is added with phosphorous oxychloride (0.01 mole). The resulting solution is stirred for 5 minutes at 0°C, 10 minutes at 25°C and 15 minutes at 80°C. After cooling to room temperature, 5 ml of N HCl are added and the mixture is refluxed for 5 minutes. 1(p-Fluorobenzyl)-4-cyano-5-amino-1,2,3-triazole separates from the cooled solution (90% yield).
M.p. 185-186°C; ^{1}H NMR (DMSO-d_6): 7.3-7.0 (m,6H); 5.5 (s,2H); IR (KBr) : 3400, 3220, 2220, 1655 cm-1.

Analogously, the following compounds were prepared:

1- or 2-benzyl-4-cyano-5-amino-1,2,3-triazole
1- or 2-(o-fluorobenzyl)-4-cyano-5-amino-1,2,3-triazole
1- or 2-(p-fluorobenzyl)-4-cyano-5-amino-1,2,3-triazole

1- or 2-butyl-4-cyano-5-amino-1,2,3-triazole

1- or 2-isopentyl-4-cyano-5-amino-1,2,3-triazole

1- or 2-(2-methoxyethyl)-4-cyano-5-amino-1,2,3-triazole

1- or 2-heptyl-4-cyano-5-amino-1,2,3-triazole

1- or 2-octyl-4-cyano-5-amino-1,2,3-triazole.

Example 5

The preparation of ethoxymethyleneamino heterocycles of formula IV is performed refluxing the respective ortho-aminonitrile with ethyl orthoformate. By way of example, the preparation of 4-cyano-5-(ethoxymethyleneamino)-1-butylpyrazole is reported.

A solution of 4-cyano-5-amino-1-butylpyrazole (20 mmols) in triethyl orthoformate (40 ml) is heated to the reflux temperature under nitrogen atmosphere for 8h. The orthoformate excess is evaporated to dryness under vacuum and the residual yellow oil is dissolved in ethyl ether and eluted through silica gel to give the pure compound (87% yield). In many cases, the residue obtained after evaporation of the orthoformate is substantially pure and is used as such in the subsequent step.

IR (nujol): 3140, 2240, 1640 cm-1; ^{1}H NMR ($CDCl_3$): 8.4 (s,1H); 7.9 (s,1H); 4.5 (t,2H); 4.3 (q,2H); 1.8 (m,2H); 1.5 (m,2H); 1.4 (t,3H); 0.9 (t,3H).

Example 6

A solution of the ethoxymethyleneamino heterocycle (20 mmols) and 2-furoic acid hydrazide (2.5 g, 22 mmols) in 2-methoxyethanol (50 ml) is refluxed for 5-10h. After cooling, the solution is evaporated to dryness to obtain a residual oil which is subjected to thermal cyclization in diphenyl ether (50 ml) using a

round-bottom flask fitted with a Dean-Stark apparatus, to remove azeotropically the water formed during the reaction. After varying times (3-5h) the reaction is checked by TLC (2:1 ethyl acetate:petroleum ether) and when the whole starting product has disappeared, the mixture is cooled and added with hexane. The resulting precipitate is filtered and crystallized from the suitable solvent. In some cases, from the solution a viscous oil separates which is decanted and subsequently extracted. The oily residue is then chromatographed on silica gel, eluting with ethyl acetate/petroleum ether mixtures, to give the tricyclic compound VI.

By way of examples, the analytical and spectroscopical characteristics of some compounds prepared by these procedures are reported:

7-butyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine.

^1H NMR (DMSO-d_6): 9.6 (s,1H); 8.6 (s,1H); 8.0 (m,1H); 7.4 (m,1H); 6.7 (m,1H); 4.5 (t,2H); 1.9 (m,2H); 1.3 (m,2H); 0.9 (t,3H).

8-butyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine.

^1H NMR (DMSO-d_6): 9.4 (s,1H); 8.9 (s,1H); 8.0 (m,1H); 7.3 (m,1H); 6.2 (m,1H); 4.5 (t,2H); 1.9 (m,2H); 1.3 (m,2H); 0.9 (m,3H). In the 2D-NMR (NOESY) spectrum, the N-CH2 signal resonating at 4.5 shows cross peaks with the C9-H signal resonating at 8.9.

7-isopentyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine.

^1H NMR ($CDCl_3$) : 9.1 (s,1H); 8.8 (s,1H); 7.7 (m,1H); 7.3 (m,1H); 6.6 (m,1H); 4.6 (t,2H); 1.18-1.7 (m,3H);

1.0 (d,6H).

8-isopentyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine.

9.1 (s,1H); 8.8 (s,1H); 7.7 (m,1H); 7.3 (m,1H); 6.6 (m,1H); 4.6 (t,2H); 1.9-1.5 (m,3H); 1.0 (d,6H).

Following this procedure, the following compounds were prepared:

7-methyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine

8-methyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine

7-(2-chlorophenyl)-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine

7-phenylethyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine

7-tert-butyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine

7-(2-cyclopentyl)ethyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine

8-benzyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine

7-benzyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

7-(2-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

7-(4-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

7-butyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

7-isopentyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

7-(2-methoxy)ethyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

7-heptyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

7-octyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

8-benzyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

8-(2-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

8-(4-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

8-butyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

8-isopentyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

8-hexyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

8-heptyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

8-octyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine

9-benzyl-2(2-furyl)-1,2,3-triazolo[4,5-e]1,2,4-triazolo[1,5-c]pyrimidine

9-(2-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[4,5-e]1,2,4-triazolo[1,5-c]pyrimidine

9-(4-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[4,5-e]1,2,4-triazolo[1,5-c]pyrimidine

Example 7

The compounds of formula VII were prepared according to two methods:

a) by hydrolysis of compounds of formula VI with diluted hydrochloric acid;

b) by thermal cyclization of heterocyclic ortho-amino-nitriles of formula III with 2-furoic acid hydrazide in diphenyl ether at a temperature of 260°C .

A) a suspension of the tricyclic compound VI (10 mmols) in 10% HCl (50 ml) is heated to the reflux temperature under stirring for 3h. After cooling, the mixture is alkalinized with concentrated ammonium hydroxide at 0°C and the resulting precipitate is recovered by filtration or extracted with ethyl acetate (3 x 100 ml), dried and evaporated to dryness under vacuum.

The residue is purified by either crystallization from the suitable solvents or chromatographed over a silica gel column eluting with ethyl acetate and petroleum ether.

1-t-butyl-4-[3(2-furyl)-1,2,4-triazol-5-yl]-4-amino-pyrazole

^1H NMR ($CDCl_3$): 13.9 (sb,1H); 7.8 (s,1H); 7.7 (s,1H); 6.9 (m,1H); 6.6 (s,1H); 6.1 (s,2H); 1.6 (s,9H).

B) A suspension of the heterocyclic ortho-amino-nitriles (20 mmols) and 2-furoic acid hydrazide (22 mmols) in diphenyl ether (30 ml) is stirred and heated to reflux (260°C) with a Dean-Stark apparatus until the starting compound has disappeared (TLC, 1-2h). After cooling, the mixture is diluted with petroleum ether and the resulting precipitate is either filtered or separated by decantation and chromatographed on a silica gel column eluting with 2:1 ethyl acetate and petroleum ether.

1-p-fluorobenzyl-4[3(2-furyl)-1,2,4-triazol-5-yl]-5-

amino-1,2,3-triazole: ^1H NMR (DMSO-d_6): 14.5 (s,1H); 7.8 (s,1H); 7.4-7.1 (m,5H); 6.6 (s,1H); 6.5 (s,2H); 5.5 (s,2H).

Example 8

A suspension of the amines of formula VII (10 mmols) in N-methyl-pyrrolidone (40 ml) is added with cyanamide (60 mmols) followed by p-toluenesulfonic acid (15 mmols). The mixture is heated to 160°C with magnetic stirring. After 4h, a second portion of cyanamide (60 mmols) is added and heating is continued overnight. The mixture is then treated with hot water (200 ml) and the precipitated solid is filtered, washed with water and crystallized from ethanol. If no precipitations take place, the solution is extracted with ethyl acetate (4 x 100 ml), the extracts are washed with brine (2 x 50 ml), dried and evaporated to dryness under vacuum. The residue is then chromatographed on a silica gel column eluting with ethyl acetate.

In the following, the analytical and spectroscopical data of some compounds prepared by this procedure are reported:

5-amino-7-butyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine (Compound 292).

M.p. 157-158°C; ^1H NMR (DMSO-d_6) : 8.1 (s,1H); 8.0 (s,2H); 7.9 (m,1H); 7.2 (m,1H); 6.7 (m,1H); 4.2 (t,2H); 1.9 (m,2H); 1.5 (m,2H); 0.9 (t,3H).

5-amino-8-butyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine (Compound 294).

M.p. 183-185°C; ^1H NMR (DMSO-d_6): 8.6 (s,1H); 8.0 (s,1H); 7.6 (s,2H); 7.2 (m,1H); 6.7 (m,1H); 4.2 (t,2H); 1.8 (m,2H); 1.2 (m,2H); 0.9 (t,3H).

5-amino-7-benzyl-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]pyrimidine.

M.p. 295-297°C; ^1H NMR (DMSO-d_6): 8.5 (s,2H); 8.0 (s,1H); 7.3 (m,6H); 6.7 (m,1H); 5.7 (s,2H).

5-amino-7-o-fluoro-benzyl-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]pyrimidine

M.p. 310-312°C; ^1H NMR (DMSO-d_6): 8.5 (s,2H); 8.0 (s,1H); 7.3 (m,5H); 6.8 (s,1H); 5.75 (s,2H).

5-amino-7-methyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 210-213°C

5-amino-7-tert-butyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 238-240°C

5-amino-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 248-250°C

5-amino-7-(2-hydroxyethyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 258-260°C

5-amino-7-phenyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 295-297°C

5-amino-7-isopentyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 208-210°C (Compound 319).

5-amino-8-isopentyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 200-203°C (Compound 320).

5-amino-7-phenethyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 225°C (Compound 341).

5-amino-7β-benzyloxyethyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine.

5-amino-7-[β-(4-isobutylphenethyl)]-2-(2-furyl)-pyrazole[4,3-e]-1,2,4-triazole[1,5-c]pyrimidine m.p. 207-210°C.

Example 9

A suspension of sodium azide (0.23 mole, 15 g) and p-fluorobenzyl chloride (0.15 mole, 18.8 ml) in absolute ethanol (45 ml) is stirred and heated to reflux overnight. After cooling, the suspension is poured into water (200 ml) and from the solution an oil separates which is extracted with ethyl acetate (3 x 100 ml), dried over sodium sulfate and evaporated under vacuum with a bath temperature below 35°C. The residue (20 g, 90%) is used directly in the subsequent step, after IR checking for the presence of the characteristic band of the azido group at 2140 cm^{-1}.

Analogously, starting from ß-phenylethanol tosylate in DMF, the 1-ß-phenethylazide is obtained.

Example 10

p-Fluorobenzylazide (15.1 g, 0.1 mole) and cyanacetamide (10.8 g, 0.13 moles) are added in this order to a suspension of powdered potassium carbonate (57.5 g, 0.42 mole) in dimethylsulfoxide (150 ml).

The mixture is stirred at room temperature for 1h. The mixture is poured into 3 l of water and the solid which separates is filtered and washed thoroughly with water to give 22.47 g (96%) of 1-p-fluorobenzyl-4-carboxamido-5-amino 1,2,3-triazole.

M.p.: 198-199°C; ^1H NMR (DMSO-d_6): 7.5-7.1 (m,6H); 6.4 (s,2H); 5.4 (s,2H).

Analogously, 2-fluoro-6-chlorobenzyl-4-carbossamide-5-amino 1,2,3-triazole; m.p. 230-231°C; ^1H-NMR (DMSO-d_6): 5.40 (s, 2H); 6.52 (sb, 2H); 7.12-7.45 (m, 5H).

3-fluorobenzyl-4-carboxamido-5-amino 1,2,3-triazole; m.p. 211-211°C ^1H-NMR (DMSO-d_6): 5.46 (s, 2H); 6.47

(sb, 2H); 7.00-7.52 (m, 6H).

2-fluorobenzyl-4-carboxamido-5-amino 1,2,3-triazole; m.p. 195-197°C.

1-(8-phenylethyl)-4-carboxamido-5-amino-1,2,3-triazole; m.p. 181-183°C; ^{1}H-NMR (DMSO-d_6): 3.04 (t, 2H); 4.35 (t, 2H); 6.30 (sb, 2H); 7.20-7.47 (m, 7H) are obtained.

Example 11

A suspension of 1-p-fluorobenzyl-4-carboxamido-5-amino-1,2,3-triazole (23.4 g, 0.1 mole) in DMF (100 ml), magnetically stirred at 0°C, is added with 20.8 ml (0.2 mole) of $POCl_3$. The solution is stirred for 5' at 0°C, 10' at room temperature and finally 15' at 80°C. After cooling, N HCl (100 ml) is added thereto and the resulting solution is refluxed for 5'; upon cooling 1-p-fluorobenzyl-4-cyano-5-amino-1,2,3-triazole (18.54 g, 90%) precipitates. M.p. 185-186°C; ^{1}H NMR (DMSO-d_6): 7.3-7.0 (m,6H); 5.5 (s,2H); IR (KBr): 3400, 3220, 2220, 1655 cm-1.

Analogously, the following compounds are obtained:

2-fluoro-6-chlorobenzyl-4-cyano-5-amino-1,2,3-triazole; m.p. 181-185°C ^{1}H-NMR (DMSO-d_6): 5.40 (s, 2H); 7.26-7.50 (m, 5H).

3-fluorobenzyl-4-cyano-5-amino-1,2,3-triazole; m.p. 195-197°C ^{1}H-NMR (DMSO-d_6): 5.44 (s, 2H); 7.00-7.43 (m, 6H).

2-flurobenzyl-4-cyano-5-amino-1,2,3-triazole; m.p.: 195-197°C.

1-(8-phenylethyl)-4-cyano-5-amino-1,2,3-triazole; m.p. 149-150°C ^{1}H-NMR (DMSO-d_6): 3.04 (t, 2H), 4.36 (t, 2H); 7.03 (sb, 2H); 7.23-7.28 (m, 5H).

Example 12

A suspension of 1-p-fluorobenzyl-4-cyano-5-amino-1,2,3-triazole (20 mmols) and 2-furoic acid hydrazide (22 mmols) in diphenyl ether (30 ml) is stirred and heated to reflux (260°C) with a Dean-Stark apparatus until the starting compound disappears (TLC, 1-2h). After cooling, the mixture is diluted with petroleum ether and the resulting precipitate is either filtered or separated by decantation and chromatographed on a silica gel column eluting with 2:1 ethyl acetate and petroleum ether.

1-p-fluorobenzyl-4[3(2-furyl)-1,2,4-triazol-5-yl]-5-amino-1,2,3-triazole; m.p. 266-268°C ^{1}H NMR (DMSO-d_6): 14.5 (s,1H); 7.8 (s,1H); 7.4-7.1 (m,5H); 6.6 (s,1H); 6.5 (s,2H); 5.5 (s, 2H). Analogously, the 1-(β-phenylethyl)-4[3(2-furyl)-1,2,4-triazol-5-yl]-5-amino-1,2,3-triazole (50%); m.p. 200-202°C 1H-NMR (DMSO-d6): 3.07 (t, 2H); 4.16 (t, 2H); 5.50 (sb, 2H); 6.61 (s, 1H); 6.95 (s, 1H); 7.2-7.4 (m, 5H); 7.78 (s, 1H); 13.8 (sb, 1H) is obtained.

Example 13

A suspension of 1-p-fluorobenzyl-4[3(2-furyl)-1,2,4-triazol-5-yl]-5-amino-1,2,3-triazole (0.325 g, 1 mmols) in N-methyl-pyrrolidone (4 ml) is added with cyanamide (6 mmols) followed by p-toluenesulfonic acid (1.5 mmols). The mixture is heated at 160°C with magnetic stirring. After 4h, a second portion of cyanamide (6 mmols) is added and heating is continued overnight. The mixture is then treated with hot water (20 ml) and the precipitated solid is filtered, washed with water and crystallized from ethanol. If no precipitations

take place, the solution is extracted with ethyl acetate (4 x 10 ml), the extracts are washed with brine (2 x 5 ml), dried and evaporated to dryness under vacuum. The residue is then chromatographed on a silica gel column eluting with ethyl acetate to give 105 mg (30% yield) of 5-amino-7-p-fluoro-benzyl-2-(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine M.p.: 266-268°C; ^{1}H NMR (DMSO-d_6) : 8.5 (sb, 2H); 7.95 (s, 1H); 7.4-7.1 (m, 6H); 6.7 (s, 1H); 5.7 (s, 2H) (Compound 340).

Analogously, were obtained:

5-amino-7-o-fluorobenzyl-2-(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine; m.p. 310°C.

5-amino-7-benzyl-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]pyrimidine; m.p. 295-7°C.

5-amino-7-(2-fluoro-6-chlorobenzyl)-2-(2-furyl)-1,2,3-triazolo5,4-e]1,2,4-triazolo[1,5-c]pyrimidine; m.p. 218-220°C; ^{1}H-NMR (DMSO-d_6): 8.51 (sb, 2H); 7.98 (s, 1H); 7.55-7.28 (m, 4H); 6.77 (m, 1H); 5.73 (s, 2H).

5-amino-7-(m-fluorobenzyl)-2-(2-furyl)1,2,3-triazolo[5,4-e] 1,2,4-triazolo[1,5-c]pyrimidine; m.p. 280-283°C; ^{1}H-NMR (DMSO-d_6): 8.45 (sb, 2H); 7.98 (s, 1H); 7.4-7.1 (m, 5H); 6.76 (s, 1H); 5.75 (s, 2H).

5-amino-7-(β-phenylethyl)-2-(2-furyl)-1,2,3-triazolo[5,4-e] 1,2,4-triazolo[1,5-c]pyrimidine; m.p. 269-271°C; ^{1}H-NMR (DMSO-d_6): 8.4 (sb, 2H); 7.98 (s, 1H); 7.3-7.15 (m, 6H); 6.8 (s, 1H); 4.71 (t, 2H); 3.31 (t, 2H) (Compound 376) are obtained.

Example 14

A suspension of anhydrous potassium carbonate (30 mmols) in anhydrous DMF (50 ml) is added with 5-amino-

4-cyano-triazole (20 mmols), prepared according to the procedures by Regitz et al. Bull. Soc. Chim. 1975, 1219, and the mixture is heated to a temperature of 80°C for 30 minutes. The suspension is added with p-fluorobenzyl chloride (25 mmols) and heated for 2 h at 80°C. After cooling to room temperature, solvent is evaporated to dryness under vacuum and the resulting residue is taken up into distilled water (100 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts are dried over anhydrous sodium sulfate and evaporated to dryness under vacuum. The resulting residue is chromatographed on a silica gel column with mixtures of ethyl acetate and hexane, to give 2-p-fluorobenzyl-5-amino-4-cyano-2H-1,2,3-triazole (49%). M.p.: 127-128°C; Anal. $C_{10}H_8FN_5$ (C, H, N); NMR (DMSO-d_6): 7.4-7.1 (m, 4H); 6.2 (sb, 2H, changeable with D_2O); 5.45 (s, 2H).

Example 15

A suspension of 2-p-fluorobenzyl-5-amino-4-cyano-2H-1,2,3-triazole (20 mmols) and 2-furoic acid hydrazide (22 mmols) in diphenyl ether (30 ml) is stirred and heated to reflux (260°C) with a Dean-Stark apparatus until the starting compound disappears (TLC, 1 hour). After cooling, the mixture is diluted with petroleum ether and the resulting precipitate is either filtered or separated by decantation and chromatographed on a silica gel column eluting with 2:1 ethyl acetate and petroleum ether.

M.p.: 223-225°C; 2-p-fluorobenzyl-4-[3(2-furyl-1,2,4-triazol-5-yl]-5-amino-2H-1,2,3-triazole: ^1H NMR (DMSO-d_6): 14.6 (sb, 1H); 7.86 (s, 1H); 7.4-7.1 (m, 5H); 6.67

(s, 1H); 5.72 (sb, 2H); 5.47 (s, 2H).

Example 16

A suspension of 2-p-fluorobenzyl-4[3(2-furyl)-1,2,4-triazol-5-yl]-5-amino-2H-1,2,3-triazole (0.325 g, 1 mmols) in N-methyl-pyrrolidone (4 ml) is added with cyanamide (6 mmols) followed by p-toluenesulfonic acid (1.5 mmols). The mixture is heated to 160°C with magnetic stirring. After 4 hours, a second portion of cyanamide (6 mmols) is added and heating is continued overnight. The mixture is then treated with hot water (20 ml) and the precipitated solid is filtered, washed with water and crystallized from DMF/H_2O. The crystallization mother solution is extracted with ethyl acetate (4 x 10 ml), the extracts are washed with brine (2 x 5 ml), dried and evaporated to dryness under vacuum. The residue is then chromatographed on a silica gel column eluting with ethyl acetate, to give 105 mg (yield 30%) of 5-amino-8-p-fluorobenzyl-2-(2-furyl)-1,2,3-triazolo-[5,4-e]1,2,4-triazolo[1,5-c] pyrimidine.

M.p.: >285°C; ^1H NMR (DMSO-d_6): 8.05 (sb, 2H); 7.95 (s, 1H); 7.5-7.2 (m, 6H); 6.75 (s, 1H); 5.84 (s, 2H) (Compound 363).

Example 17

A suspension stirred and cooled at 0°C of 80% NaH (1.5 moles) in anhydrous DMF (30 ml) is added with a solution of 4-cyano-5-tosylamino-1,2,3-triazole (1 mmole) in anhydrous DMF (5 ml). The mixture is left to react at room temperature for 1 h, after that p-fluorobenzyl chloride (0.90 mmole) is added. The resulting suspension is heated at 80°C overnight. The mixture is evaporated to dryness and the residue taken up into wa-

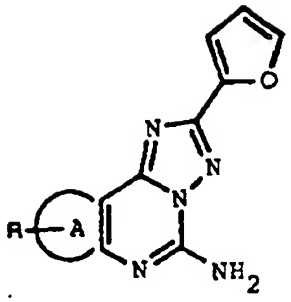
ter and extracted with ethyl acetate (3 x 30 ml). The combined organic extracts are dried over sodium sulfate and evaporated to dryness. The oily residue is crystallized from dioxane/water, to give 1-p-fluorobenzyl-5-cyano-4-tosylamino-1-H-1,2,3-triazole in a 56% yield.
M.p.: 163-165°C; ^{1}H NMR ($CDCl_3$): 7.8-7.7 (m, 2H); 7.26-7.05 (m, 7H); 5.49 (s, 2H); 2.37 (s, 3H).

Example 18

1-p-Fluorobenzyl-4-amino-5-cyano-triazole is prepared according to the procedures described by Regitz et al. Liebigs Ann. Chem. 1975, 2159-2168, by acid hydrolysis with concentrated sulfuric acid of the compound of example 17, at -15°C.
M.p.: 105-108°C; ^{1}H NMR (DMSO-d_6): 7.44-7.19 (m, 4H); 6.27 (sb, 2H); 5.51 (s, 2H).

CLAIMS

1. Compounds of formula I:



I

in which:

A is a pyrazole, imidazole or triazole ring;

R is hydrogen; C_1-C_8 alkyl; C_3-C_7 alkenyl, C_3-C_7 alkynyl; C_3-C_7 cycloalkyl; C_1-C_5 alkyl substituted with one or more halogen atoms, hydroxy groups, C_1-C_4 alkoxy, C_3-C_7 cycloalkyl, groups of formula $-NR_1R_2$, $-CONR_1R_2$; aryl optionally substituted with halogen atoms, C_1-C_4 alkoxy groups, C_1-C_4 alkyl, nitro, amino, cyano, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, carboxy, carboxyamido; C_7-C_{10} aralkyl in which the aryl moiety can be substituted with one or more of the substituents indicated above for the aryl group; a group of formula $-(CH_2)_m$-Het, wherein Het is a 5-6 membered aromatic or non aromatic heterocyclic ring containing one or more heteroatoms selected from N, O, S and m is an integer from 1 to 5;

R_1, R_2, which are the same or different, are hydrogen, C_1-C_5 alkyl, C_7-C_{10} aralkyl, phenyl, or taken together with the nitrogen atom they are linked to, they form an azetidine ring or a 5-6 membered heterocyclic ring con-

taining one or more heteroatoms such as N, O, S and n is an integer from 2 to 5, with the proviso that, when A is a pyrazole or imidazole, R is different from fluorobenzyl.

2. Compounds according to claim 1, wherein A is a triazole ring.

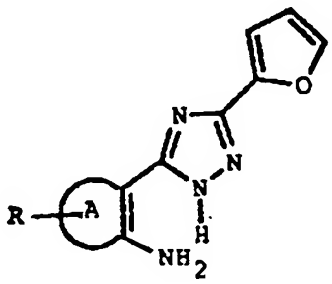
3. Compounds according to claim 1, wherein A is a pyrazole ring.

4. Compounds according to claim 1, wherein A is an imidazole ring.

5. Compounds according to any one of the above claims, wherein R is hydrogen, C_1-C_8 alkyl, aryl or C_7-C_{10} aralkyl, optionally substituted with halogen atoms.

6. Compounds according to any one of the above claims wherein R is phenethyl in which the phenyl ring may optionally be substituted by one or more substituents selected from chlorine, fluorine atoms, methoxy, nitro, cyano, methyl, trifluoromethyl, difluoromethoxy groups.

7. A process for the preparation of the compounds of formula I which comprises reacting a compound of formula VII



VII

wherein R and A are as defined above, with cyanamide.

8. Pharmaceutical compositions containing as the active ingredient one compound of claims 1-6 in admixture with an acceptable carrier.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 94/02031

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/14 A61K31/495 //(C07D487/14,239:00,249:00,249:00), (C07D487/14,231:00,239:00,249:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 263 071 (CIBA GEIGY AG) 6 April 1988 Compounds (Ib) see page 7, line 8 - line 9	1-8
Y	EP,A,0 217 748 (CIBA GEIGY AG) 8 April 1987 Compounds (Ic) see page 5, line 64 - line 65	1-8
Y	EUR. J. MED. CHEM. vol. 28 , 1993 pages 569 - 576 GATTA ET AL 'Synthesis of imidazo [1,2-c]pyrazolo[4,3-e]pyrimidines' cited in the application Compounds 13e,13f,19e,19f	1-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 September 1994	12. 10. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Gettins, M

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 94/02031

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J.MED.CHEM. vol. 31 , 1988 pages 1014 - 1020 FRANCIS ET AL 'Structure-Activity Profile of a Series of Novel Triazoloquinazoline Adenosine Antagonists.' cited in the application Compound 2a see page 1015	1-8
A	US,A,4 713 383 (FRANCIS) 15 December 1987 see claim 10	1-8

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ..nal Application No
PCT/EP 94/02031

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0263071	06-04-88	US-A-	4831013	16-05-89
		AU-B-	612331	11-07-91
		AU-A-	8027187	21-04-88
		CA-A-	1317590	11-05-93
		DE-A-	3781080	17-09-92
		WO-A-	8802370	07-04-88
		ES-T-	2051772	01-07-94
		JP-T-	1500996	06-04-89
EP-A-0217748	08-04-87	JP-A-	62135475	18-06-87
		US-A-	4831013	16-05-89
US-A-4713383	15-12-87	AU-A-	4813285	10-04-86
		EP-A-	0181282	14-05-86
		JP-A-	61165386	26-07-86